Open Journal of Composite Materials, 2024, 14, 109-123
https://www.scirp.org/journal/ojcm
ISSN Online: 2164-5655
ISSN Print: 2164-5612

One-Pot Green Synthesis of 1,4-Dihydropyridine Derivatives Using Polyindole TiO_2 Nanocatalyst by Solvent Free Method

Deepak Babasaheb Phasage[1], Sanjay K. Sharma[1], Balram Tripathi[2], Sonia Chahar Srivastava[2]*

[1]Department of Chemistry, JECRC University Jaipur, India
[2]S. S. Jain Subodh PG College, Jaipur, India
Email: *schahar1617@gmail.com

How to cite this paper: Phasage, D.B., Sharma, S.K., Tripathi, B. and Srivastava, S.C. (2024) One-Pot Green Synthesis of 1,4-Dihydropyridine Derivatives Using Polyindole TiO_2 Nanocatalyst by Solvent Free Method. *Open Journal of Composite Materials*, **14**, 109-123.
https://doi.org/10.4236/ojcm.2024.143008

Received: March 12, 2024
Accepted: June 11, 2024
Published: June 14, 2024

Abstract

This study used a Polyindole in combination with TiO_2 nanocatalyst as an efficient heterogeneous catalyst to carry out a multi-component Hantzsch reaction involving different aromatic aldehydes with methyl acetoacetate, and aqueous ammonium to create 1,4-dihydropyridine derivatives under solvent free condition at ambient temperature. A broad range of aldehydes and methyl acetoacetates, ranging from heteroaromatic to polyaromatic one, with high level of functional group tolerance can be used to provide the desired products possessing relevant medicinal moiety in high yields. This technology has prospective advantages over current protocols, including the utilization of a cheap, stable, recyclable, and safe catalyst, quicker reaction times with higher yields and simple product isolation.

Keywords

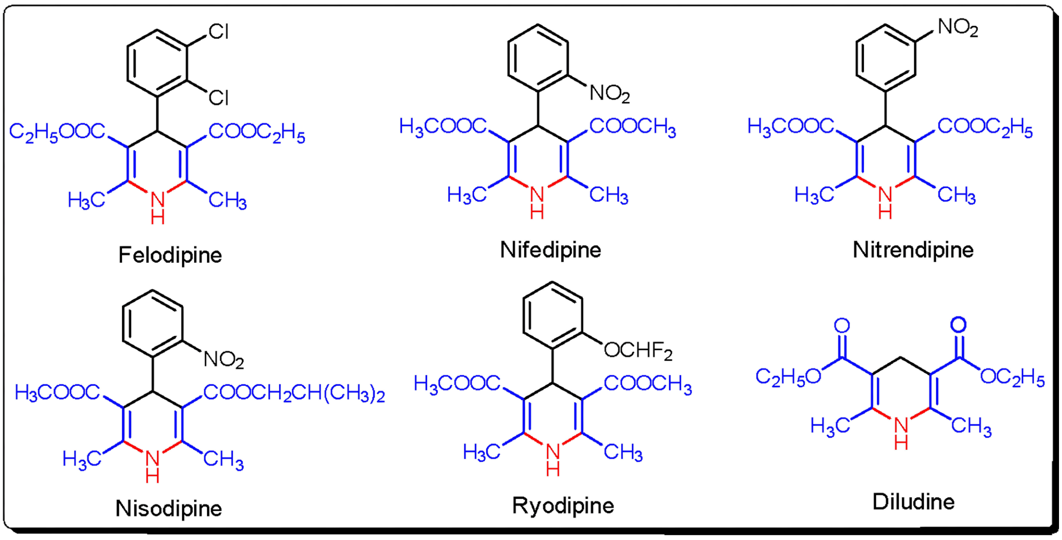
TiO_2, Nanocatalyst, Green Synthesis, Surface Morphology

1. Introduction

1,4-dihydropyridine scaffolds represents heterocyclic unit of remarkable biological and pharmacological efficiency [1]. More than a hundred years ago, 1,4-dihydropyridine derivatives was reported by Arthur Hantzsch [2]. These are important precursors due to their pharmacological and biological activities such as antihypertensive [3], anti-anginal and as calcium channel blockers [4] [5] [6] [7] [8] for the treatment of cardiovascular diseases [9]. A number of DHP derivatives are employed as potential drug candidates for the treatment of congestive heart failure, and also acts as NADH mimics for the reduction of carbonyl compounds and their derivatives. Apart from these 1,4-DHP also possess many more pharmacological activities such as anti-bacterial, anti-cancer, anti-microbial, anti-tubercular, antioxidant agents, antiulcer, CFTR, antimalarial and HIV-I protease inhibitory and many more (**Scheme 1**) [10] [11] [12].

The biological activity of 1,4-dihydropyridine derivatives in numerous sectors has recently gained significant attention, which have persuaded scientists to develop novel new processes for synthesizing them. 1,4-dihydropyridine generally synthesized by condensation of aldehydes, β-ketoester and ammonia or ammonium acetate. The number of attempts has been taken to improve the yield and selectivity of the product under milder condition of this Hantzsch reaction using different alternate process in the literature. All of these aforesaid reaction required one of the following conditions like microwave [13] [14] [15], ionic liquids [16] and higher temperature [17] [18] [19], ultrasound irradiation, catalyst or reagents like TMSl [20], Molecular Iodine [21], Yb(OTf)$_3$ [22], FeCl$_3$ [23], Ceric Ammonium Nitrate [24], Silica gel supported sodium bisulfate [25] and Scandium (III) triflate [26]. However, all of these methods have some drawbacks, such as the use of hazardous solvents, extended heating, tiresome work-up, by-products, and limited yield.

In a recent year, Nano catalytic approach for the synthesis of 1,4-dihydropyridine is more advantageous over conventional method due to its enormous activity and selectivity. This methodology becomes green, non-toxic and eco-friendly process. To this content, Safari *et al.* in 2011, introduce Cobalt nanoparticles catalysed synthesis of 1,4-dihydropyridine [27]. In 2012, Tajbakhsh *et al.* and co-workers reported that TiO$_2$ has been used as a catalyst in the production of Dihydropyridine [28]. In the same year Yang *et al.* synthesiszed the 1,4-dihydropyridine using magnetic nanocrystalline Fe$_3$O$_4$ as catalyst [29]. Further, synthesis of 1,4-dihydropyridine derivatives *via* one pot condensation of dimedone or



Scheme 1. Some commercial drugs containing the 1,4-dihydropyridine core moieties.

4-hydroxycumarine, aldehydes and ammonium acetate using $Fe_3O_4@SiO_2$ nanoparticles as a heterogeneous catalyst in 2014 by Dam *et al.* [30]. Alinezhad *et al.* reported synthesis of 1,4-dihydropyridine using Cu-doped ZnO nanocrystalline powder as a heterogeneous catalyst [31]. Bajajand and co-workers report CuO nanoflakes for the synthesis of 1,4-dihydropyridine [32]. Dehghanizadeh *et al.* used zinc oxide nanoparticles as heterogeneous nanocatalyst for the synthesis of 1,4-dihydropyridine [33]. A Nickel oxide loaded on Zirconia (NiO/ZrO_2) as a nano catalyst for synthesis of 1,4-dihydropyridine reported by Bhaskaruni *et al.* in 2019 [34]. Later, Cahyana *et al.* introduce copper iodide nanoparticles for synthesis of 1,4-dihydropyridine [35]. However, all above methods has significant drawbacks, such as a longer reaction duration, low yield, lack of recyclability, and a challenging isolation process of the desired products. These challenges encourage researcher to developed new and green synthetic approach to overcome the disadvantages associated to Hantzsch condensation. In this context, polymer supported titanium dioxide (Polyindole TiO_2) nanocatalytic systems have been developed as green, eco-friendly and reusable nanocatalyst to synthesized 1,4-dihydropyridine.

The current study describes the synthesis of polyindole-TiO_2 nanocomposites and their use as a recyclable and possible catalyst for the single-pot, multicomponent synthesis of dihydropyridine without the need of solvents. The synthesis of 1,4-dihydropyridines derivatives derived from raw materials including aldehyde, methyl acetoacetate and ammonia solution under solvent free mild green condition.

2. Results and Discussion

TiO_2 nanoparticle FTIR spectra are shown in **Figure 1(a)**. The O-H bond's stretching vibration shows band at ~3400 cm^{-1}, and the bending vibration of O-H group shows peak at 1700 cm^{-1}. The peaks identified at 461 and 501.5 cm^{-1} is due to the stretching and bending vibrations of Ti-O-Ti group. Broad band in the polyindole-TiO_2 FTIR spectrum at about 3600 cm^{-1} suggests the presence of -NH bonds (**Figure 1(b)**). The nitrogen of the indole is not the polymerization site, as indicated by the band at 1570 cm^{-1}, which is caused by stretching and deformation vibrations of the -NH bond. The benzene ring is not impacted during the polymerization of indole, according to the sharp band at 740 cm^{-1}. The stretching mode of the benzene ring, which is represented by the peaks at 1454 cm^{-1} and 1610 cm^{-1}, indicates that the benzene ring was not the site of polymerization. This indicates that polymerization occurred.

TiO_2 and polyindole-TiO_2 nanocomposites' surface morphologies were examined using scanning electron microscopy (SEM), and they are depicted in **Figure 2(a)** and **Figure 2(b)**, respectively. As shown in the SEM image, the TiO_2 nanoparticles are heavily aggregated and have a spherical morphology. **Figure 2(a)**. While the TiO_2 nanoparticles, which range in size from 40 to 60 nm, are dispersed in clusters formed by the accumulation of Polyindole particles. By

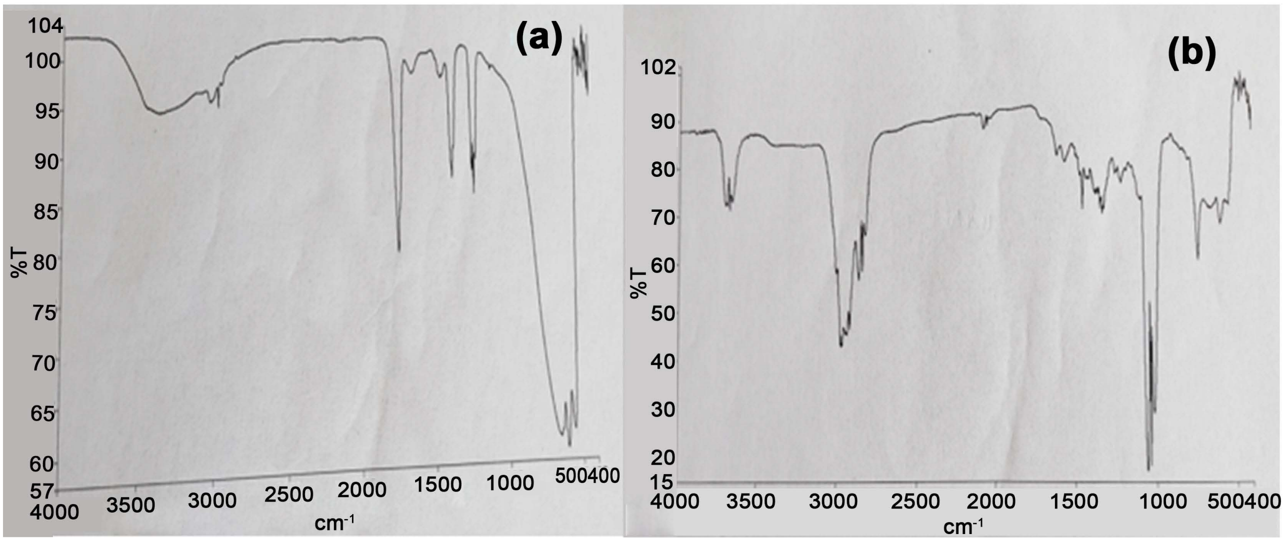


Figure 1. FT-IR spectra of (a) TiO_2 & (b) Polyindole TiO_2 (Pin-TiO_2) nanoparticles.

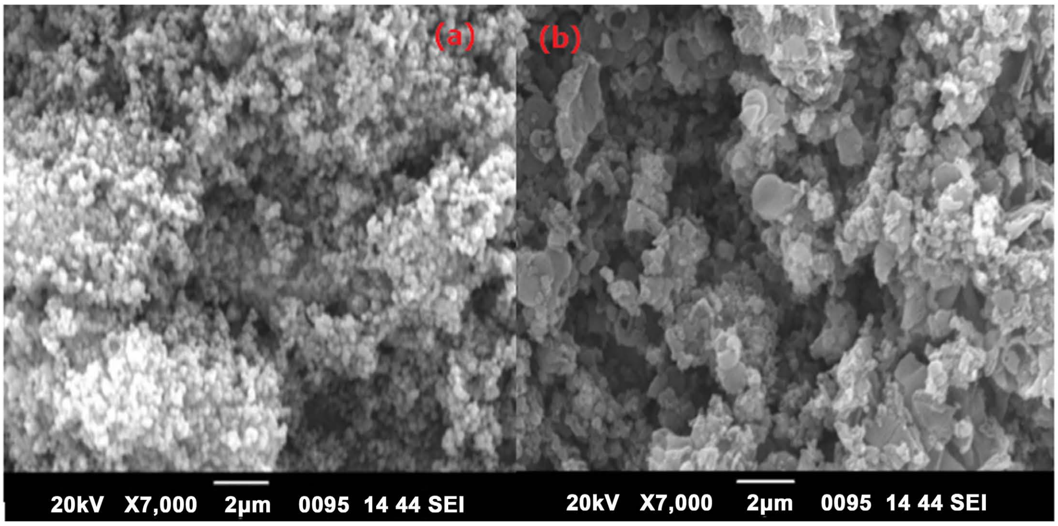


Figure 2. SEM images of (a) TiO_2 & (b) Polyindole TiO_2 (Pin-TiO_2) nanoparticles.

generating spheres, this functions as a soft template. According to SEM findings, the Polyindole matrix contains nanostructured TiO_2 particles that are evenly dispersed.

The crystal structure of Polyindole (PIn), TiO_2 and Polyindole-TiO_2 (PIn-TiO_2) are characterized by XRD. The X-ray diffraction pattern for the synthesized nano TiO_2 is shown in **Figure 3(a)**. The diffraction peak appears at 2θ values with 27.19˚, 35.89˚, 39.56˚, 40.99˚, 44.45˚ and 54.18˚ correlates the crystal planes of (110), (101), (200), (111), (210) and (211) which is matched and confirmed with the standard reference XRD pattern of TiO_2 (JCPDS Card No.21-1276). The high intense peak of the XRD pattern at 2θ value of 27.19 confirmed the prepared TiO_2 nanoparticle correlates the rutile phase and the preferred orientation plane was (110). The X-ray diffraction pattern of synthesized polyindole (PIn) as presented in **Figure 3(b)** shows broad peaks at 19.54 and 25.58˚. The presence of

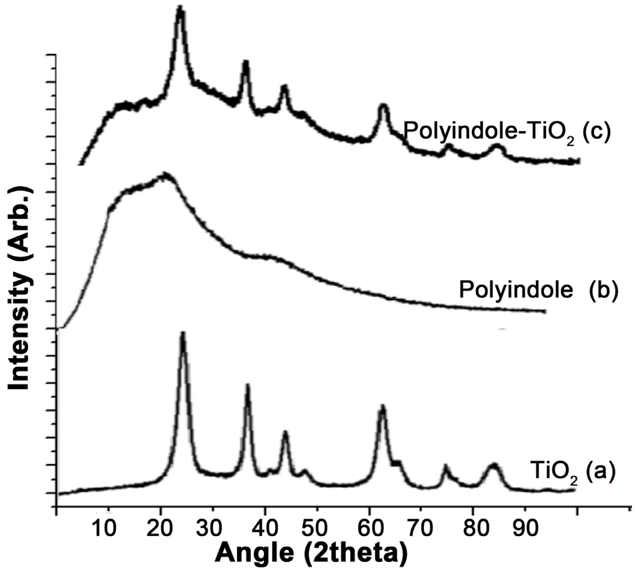


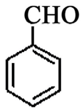
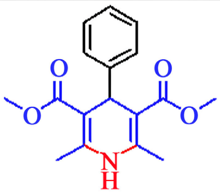
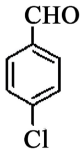
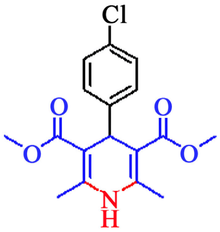
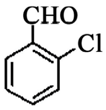
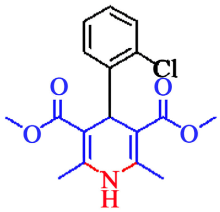
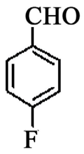
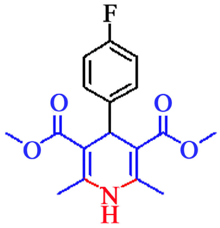
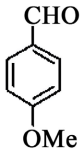
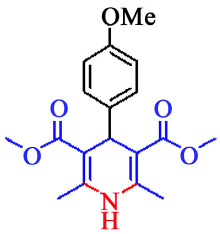
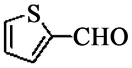
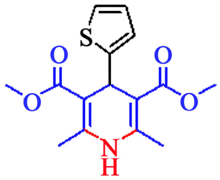
Figure 3. XRD spectra of (a) TiO_2 (b) Polyindole (c) Polyindole-TiO_2 nanoparticles.

these broad peaks confirms the polymerization of indole, and diffraction peak at 25.58˚ validates the partial crystalline nature of PIn. Strong diffraction peak at 27.19˚ in the XRD pattern of the polyindole-TiO_2 nanocomposites shown in Figure 3(c) indicate that TiO_2 is present in the nanocomposite in rutile phase.

In these efforts to develop an efficient & environmentally benign methodology for the synthesis of dihydropyridine, we initiated our studies by subjecting catalytic amount of polyindole TiO_2 to the mixture of benzaldehyde, methyl acetoacetate and ammonia solution (25%) in solvent free condition at room temperature. Unfortunately, the resulted yield was very poor even after 24 h of stirring. To increase the yield of the reaction, various solvent systems were screened at 50˚C temperature. We pleased to see that the synthesis of DHP was effective catalyzed by polyindole TiO_2 in solvent free condition at elevated temperature leading to high yield of product. The results are summarized in Table 1. It is evident that the best result was obtained by the application of 5 mol% of Polyindole TiO_2 in solvent free condition at 50˚C. Higher and lower amount of catalyst subsequently reduce the yield of the product (Table 1, entry 5). In typical procedure 1 mmole of aldehyde, 2 mmole of methyl acetoacetate and 2 mmole of ammonia solution were mixed in solvent free condition in presence of 5 mole % of polyindole TiO_2 and reaction mixture was stirred for 1 to 2 h at 50. After workup it produced the corresponding DHP's with good yield.

After having optimization condition in our hand, we further explore the substrate scope in Figure 4. Electron rich and electron deficient aromatic aldehyde as well as heterocyclic aldehyde work well with our protocol. First of all, aromatic aldehyde possessing an array of either electron donating or withdrawing substituents at both the *p* and *m*-position delivered the desired 1, 4-dihydropyridines products (**2B, 2D-E, 2G, 2H**) in excellent yields. Further, the sterically congested *o*-substituted aldehyde substrate is also suitable to produce the desired

1,4-dihydropyridines products (**2C**) in good yield. Interestingly, polyaromatic substrates like, [1,1'-biphenyl]-4-carbaldehyde were equally competent in furnishing the product **2J** in excellent yield. Pleasingly, the efficiency of this reaction was not suppressed when heteroaromatic substrates such as thiophene-2-carbaldehyde and *1H*-pyrrole-2-carbaldehyde was employed. Notably, the Poly-indole TiO_2 offers much easier recyclability than the homogeneous one (Table 2).

Entry	Aldehyde	Product	Time (h)	M.P (°C)	Yield (%)
A			1.5	191-193	98
B			1.5	196-198	96
C			2.0	144-146	85
D			1.5	171-173	90
E			2.0	180-182	97
F			1.7	197-198	95

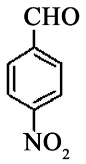
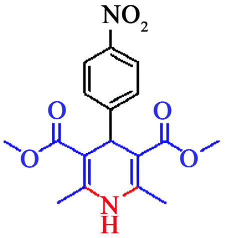
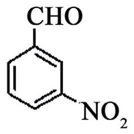
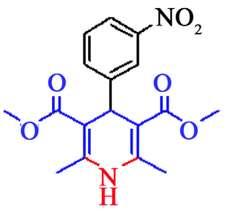
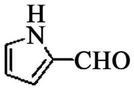
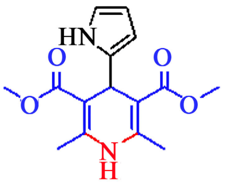
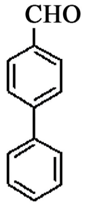
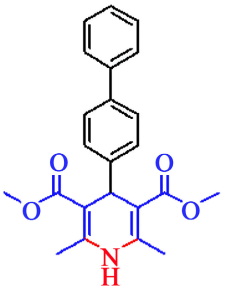
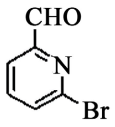
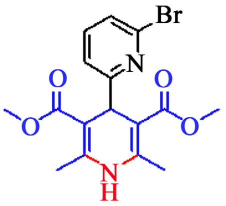
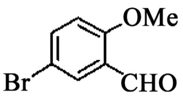
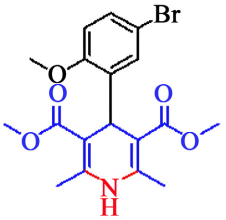
G			1.5	195-197	93
H			2.0	207-209	95
I			2.0	186-188	89
J			1.5	225-227	91
K			2.0	191-192	88
L			2.5	198-200	90

Figure 4. Substrate scope for the synthesis of 1,4-dihydropyridines derivatives[a]. [a]Reaction conditions: Aromatic aldehyde (1 mmol), methyl acetoacetate (2 mmol) and aq. ammonia solution (2 mmol), 50˚C, 1 - 2 h.

Plausible General Mechanism:

As reported in the literature, [36] the plausible mechanism for nanocatalyzed synthesis of 1,4-dihydropyridine contains the activation of aldehydes and diketones

Table 1. Optimization of reaction conditions for the synthesis of 1,4-dihydropyridines.

Entry	Catalyst (wt.%)	Solvent	Temp ˚C	Time (h)	Yield (%)[a]
1	5	Neat	RT	24	35
2	5	MeOH	RT	24	25
3	5	EtOH	RT	24	30
4	5	THF	RT	4	10
5	5	Neat	50	1.5	95
6	0	Neat	50	6.5	70
7	10	Neat	50	1.5	83
8	15	Neat	50	1.5	70
9	5	MeOH	50	4.0	75
10	5	EtOH	50	4.5	69
11	5	IPA	50	6	70

[a]Isolated yield.

Table 2. Catalyst recovery study data under optimized condition.

Entry	Time (h)	Yield (%)[a]
1st cycle	1.5	98
2nd cycle	1.5	96
3rd cycle	2.0	93
4th cycle	2.5	90
5th cycle	3.5	89
6th cycle	5.0	85

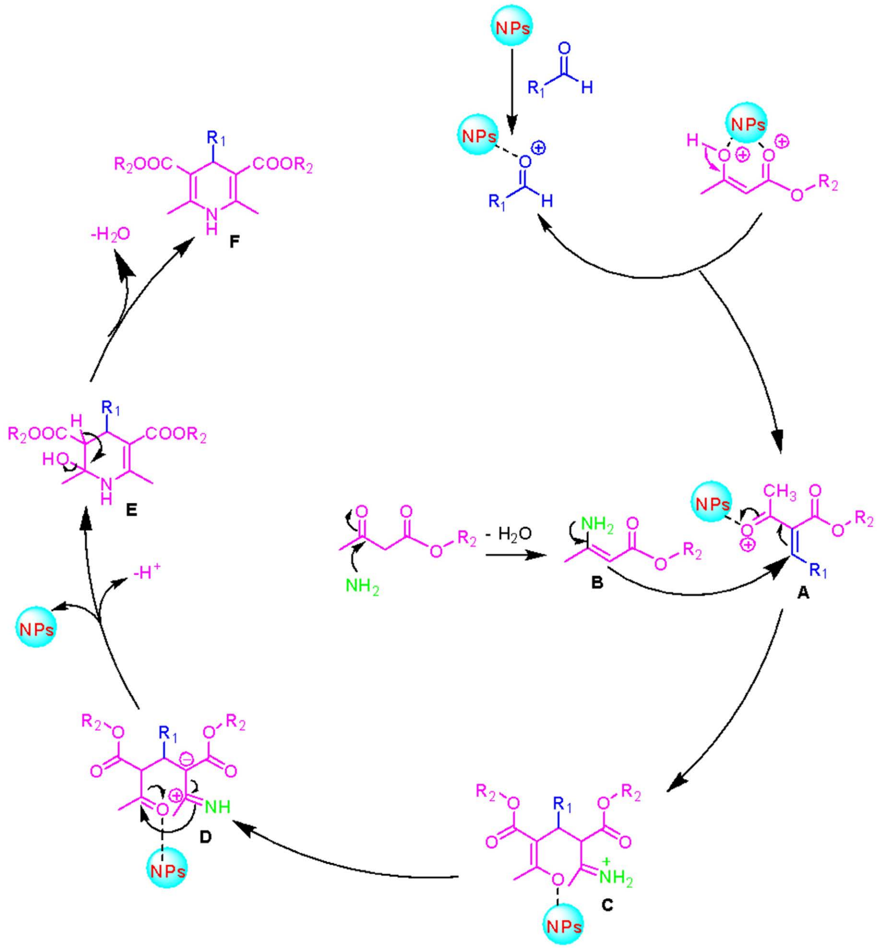
[a]Isolated yield.

by nanoparticles followed by nucleophilic attack to form intermediate A. Intermediate A was further activated by the nanoparticle and facilitated the nucleophilic attack by intermediate B to form intermediate C. After following the intra-molecular cyclization to generate intermediate D, which was further deprotonated to form intermediate E, and finally the resulting 1,4-dihydropyridine (F) is formed after dehydration of intermediate E (Scheme 2).

3. Experimental Method

General experimental description:

Chemicals, reagents and solvents were obtained from Sigma Aldrich Company. All compounds were identified by their physical and spectroscopic data. The nanomaterial has been characterized by Fourier transform infrared analysis galaxy series FT-IR 5000 spectrometer, scanning electron microscopy (SEM) by MIRA III from TESCAN Company and Philips XL30, X-ray diffraction by JEOL JDX-8030 (30 kV, 20 mA), On a Brucker spectrophotometer (400 MHz) in



Scheme 2. Plausible mechanism for synthesis of 1, 4-dihydropyridine.

DMSO-d_6 or $CDCl_3$. All the ^1H and $^{13}C\{^1H\}$ NMR spectra were referenced internally to the residual solvent signals. On an Agilent model, the mass spectra were captured. Melting points were determined uncorrected utilizing capillary tubes on an electrothermal digital instrument.

Preparation of TiO_2 Nanoparticles:

Under a nitrogen atmosphere, titanium tetrachloride ($TiCl_4$) was added drop by drop to ethanol and water (1:1) to create TiO_2 nanoparticles. At room temperature, the reaction mixture was agitated for 12 hours to produce a yellow-colored solution of TiO_2 nanoparticles. After being obtained, the nanoparticles were filtered, dried at 80˚C in an oven, and then calcined for an hour at 350˚C in a furnace.

Preparation of Polyindole-TiO_2 Nanoparticles:

The monomer indole (1 mmol) and a 5% aq hydrochloric acid solution were added to a round-bottom flask and warmed to 40˚C to form a clear solution. To this clear solution, TiO_2 nanoparticles were added, polymerization reaction was allowed to proceed for two hours. Under constant stirring, ammonium persulfate (1 mmol) solution in 10 ml de-ionised water was added dropwise to the monomer solution containing TiO_2 at 0˚C - 5˚C. The reaction mixture was allowed to stand for 12 hours at room temperature to form greenish-black precipitation of polymerized material, which was filtered and washed with cold water. The isolated polyindole-TiO_2 nanoparticles were dried under vacuum at 70˚C and characterized by FTIR, XRD, and SEM.

General procedure for the synthesis of 1,4-dihydropyridine:

A mixture of aromatic aldehyde (1 mmol), methyl acetoacetate (2 mmol), and aq. ammonia solution (2 mmol) was mixed at room temperature. The mixture was stirred for 5 minutes. Polyindole-TiO_2 Nano-PiN.TiO_2 (5%W) as a catalyst was then added, and the reaction mixture was stirred magnetically at 50˚C. The progress and completion of the reaction were monitored by TLC (*n*-hexane/ethyl acetate: 3:1 v/v) during appropriate time periods. After completion of the reaction, 5 ml of methanol was added, and the catalyst was separated by simple filtration. Filtrate was added to 15 ml of cold water, and precipitates were filtered off and washed with the cold methanol-water mixture. Further purification is done by crystallization using methanol to obtain a pure product as a solid material.

4. Spectroscopic Data for the New Compounds

Dimethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (2A):

Appearance: white solid, Melting Point: 191˚C - 193˚C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.27 - 7.25 (m, 2H), 7.23-7.21 (m, 2H), 7.15 - 7.11 (m, 1H), 5.65 (s, 1H), 5.00 (s, 1H), 3.64 (s, 6H), 2.34 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.2, 147.5, 144.3, 128.2, 127.8, 126.3, 104.1, 51.1, 39.4, 19.8 ppm. Mass (m/z): Mass (M + 1): 302.9.

Dimethyl 4-(4-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-icarboxylate (2B):

Appearance: white solid, Melting Point: 196˚C - 198˚C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.20 - 7.16 (m, 4H), 5.67 (s, 1H), 4.97 (s, 1H), 3.64 (s, 6H), 2.33 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.9, 146.1, 144.4, 132.0, 129.2, 128.3, 103.8, 51.2, 39.1, 19.8 ppm. Mass (M + 1): Mass (M + 1): 337.2.

Dimethyl 4-(2-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (2C):

Appearance: white solid, Melting Point: 144˚C - 146˚C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.35 (m, J = 7.7, 1.6 Hz, 1H), 7.23 (dd, J = 7.9, 1.1 Hz, 1H), 7.12 (td, J = 7.6, 1.1 Hz, 1H), 7.03 (td, J = 7.8, 1.6 Hz, 1H), 5.69 (s, 1H), 5.39 (s, 1H), 3.60 (s, 6H), 2.31 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.1, 146.0, 144.2, 132.5, 131.3, 129.4, 127.4, 127.0, 104.1, 51.0, 37.3, 19.6 ppm. Mass (M + 1): 337.1.

Dimethyl 4-(4-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (2D):

Appearance: off white solid, Melting Point: 171˚C - 173˚C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.22 - 7.19 (m, 2H), 6.90 - 6.86 (m, 2H), 5.81 (s, 1H), 4.97 (s, 1H), 3.64 (s, 6H), 2.32 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.1, 161.5 (d, J = 243.7 Hz), 144.3, 143.4, 129.2 (d, J = 7.8 Hz), 114.8 (d, J = 21.0 Hz), 104.0, 51.2, 38.8, 19.7 ppm. Mass (M + 1): 319.7.

Dimethyl 1,4-dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2E):

Appearance: off white solid, Melting Point: 180˚C - 182˚C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 8.3 Hz, 2H), 5.74 (s, 1H), 4.94 (s, 1H), 3.75 (s, 3H), 3.64 (s, 6H), 2.32 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.2, 158.1, 144.0, 140.1, 128.7, 113.5, 104.3, 55.3, 51.1, 38.6, 19.7 ppm. Mass (M + 1): 332.2.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(thiophen-2-yl)pyridine-3,5-dicarboxylate (2F):

Appearance: pale yellow solid, Melting Point: 197-198˚C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.86-6.84 (m, 1H), 6.78-6.77 (m, 1H), 5.92 (s, 1H), 5.33 (s, 1H), 3.71 (s, 6H), 2.34 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.8, 151.5, 145.0, 126.6, 123.4, 123.1, 103.5, 51.3, 34.4, 19.6 ppm. Mass (M + 1): 307.9.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate (2G):

Appearance: yellow solid, Melting Point: 195˚C - 197˚C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.7 Hz, 2H), 7.43 (t, *J* = 5.6 Hz, 2H), 5.81 (s, 1H), 5.10 (s, 1H), 3.64 (s, 6H), 2.35 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.6, 154.9, 146.5, 145.1, 128.7, 123.6, 103.1, 51.3, 40.0, 19.8 ppm. Mass (M + 1): 347.1, 348.2.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate (2H):

Appearance: pale yellow solid, Melting Point: 207˚C - 209˚C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (t, *J* = 2.0 Hz, 1H), 8.01-7.98 (m, 1H), 7.63 - 7.61 (m, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 5.86 (s, 1H), 5.10 (s, 1H), 3.64 (s, 6H), 2.36 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 167.6, 149.7, 148.5, 145.1, 134.3, 128.9, 122.9, 121.6, 103.3, 51.3, 39.8, 19.8 ppm. Mass (M + 1): 347.2, 348.2.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(1H-pyrrol-2-yl)pyridine-3,5-dicarboxylate (2I):

Appearance: green solid, Melting Point: 186˚C - 188˚C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 6.65-6.63 (m, 1H), 6.04 - 6.02 (m, 1H), 5.72 (s, 2H), 5.04 (s, 1H), 3.71 (s, 6H), 2.30 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.7, 145.0, 136.9, 116.7, 107.7, 104.2, 102.1, 51.5, 32.4, 19.9 ppm. Mass (M + Na): 314.2.

Dimethyl 4-([1,1'-biphenyl]-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (2J):

Appearance: white solid, Melting Point: 225˚C - 227˚C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.53 (m, 2H), 7.45 - 7.38 (m, 4H), 7.34 -

7.27 (m, 3H), 5.76 (s, 1H), 5.05 (s, 1H), 3.66 (s, 6H), 2.35 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 168.2, 146.6, 144.4, 141.3, 139.1, 128.8, 128.1, 127.1, 127.0, 127.0, 103.9, 51.2, 39.1, 19.7 ppm. Mass (M + 1): 378.1, 379.2.

Dimethyl 4-(3-bromopyridin-2-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (2K):

Appearance: Off white solid, Melting Point: 191˚C - 192˚C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.09 - 6.74 (m, 1H), 5.67 (s, 1H), 5.17 (s, 1H), 3.62 (s, 6H), 2.33 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 168.1, 167.0, 146.7, 141.6, 138.3, 126.4, 123.2, 100.8, 50.9, 43.2, 19.2 ppm. Mass (M/Z): 381.1.

Dimethyl 4-(5-bromo-2-methoxyphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (2L):

Appearance: off white solid, Melting Point: 198˚C - 200˚C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.21 - 7.18 (m, 2H), 6.68 (d, J = 8.5 Hz, 1H), 5.68 (s, 1H), 5.25 (s, 1H), 3.79 (s, 3H), 3.62 (s, 6H), 2.30 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.3, 156.1, 144.3, 137.8, 132.7, 130.2, 112.9, 112.8, 102.8, 56.0, 51.1, 34.9, 19.5 ppm. Mass (M + 1): 412.1, 413.

5. Conclusion

We present a solvent-free catalytic method for synthesizing biologically relevant dihydropyridine derivatives from aromatic aldehydes, methyl acetoacetate, and aqueous ammonium. Key aspects of this protocol include 1) The use of a recyclable catalyst; 2) Short reaction times; 3) Broad substrate compatibility with excellent functional group tolerance, yielding compounds with potential medicinal activity. Additionally, recyclability studies demonstrate that the catalyst maintains nearly unchanged catalytic activity over multiple cycles without loss of efficacy. In order to synthesis 1,4-dihydropyridine under environmentally friendly conditions, we have created stable and novel polyindole-TiO_2 nanoparticles. This approach emphasizes the beneficial features such shorter reaction times, the removal of hazardous solvents and byproducts, quick work-up, and straightforward product separation. The nano-catalyst also demonstrated good reactivity and effective catalytic recyclability.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Stout, D.M. and Meyers, A.I. (1982) Recent Advances in the Chemistry of Dihydropyridines. *Chemical Reviews*, **82**, 223-243. https://doi.org/10.1021/cr00048a004

[2] Eisner, U. and Kuthan, J. (1972) Chemistry of Dihydropyridines. *Chemical Reviews*, **72**, 1-42. https://doi.org/10.1021/cr60275a001

[3] Mannhold, R., Jablonka, B., Voigt, W., Schönafinger, K. and Schraven, E. (1992) Calcium- and Calmodulin-Antagonism of Elnadipine Derivatives: Comparative SAR. *European Journal of Medicinal Chemistry*, **27**, 229-235.

https://doi.org/10.1016/0223-5234(92)90006-m

[4] Boecker, R.H. and Guengerich, F.P. (1986) Oxidation of 4-Aryl- and 4-Alkyl-Substituted 2, 6-Dimethyl-3, 5-Bis(alkoxycarbonyl)-1, 4-Dihydropyridines by Human Liver Microsomes and Immunochemical Evidence for the Involvement of a Form of Cytochrome P-450. *Journal of Medicinal Chemistry*, **29**, 1596-1603. https://doi.org/10.1021/jm00159a007

[5] Duburs, G. and Sausins, A. (1988) Synthesis of 1, 4-Dihydropyridines by Cyclocondensation Reactions. *Heterocycles*, **27**, Article 269. https://doi.org/10.3987/rev-87-370

[6] Goldmann, S. and Stoltefuss, J. (1991) 1, 4-Dihydropyridines: Effects of Chirality and Conformation on the Calcium Antagonist and Calcium Agonist Activities. *Angewandte Chemie International Edition in English*, **30**, 1559-1578. https://doi.org/10.1002/anie.199115591

[7] Bossert, F., Meyer, H. and Wehinger, E. (1981) 4-Aryldihydropyridines, a New Class of Highly Active Calcium Antagonists. *Angewandte Chemie International Edition in English*, **20**, 762-769. https://doi.org/10.1002/anie.198107621

[8] Bossert, F. and Vater, W. (1989) 1, 4-Dihydropyridines—A Basis for Developing New Drugs. *Medicinal Research Reviews*, **9**, 291-324. https://doi.org/10.1002/med.2610090304

[9] Reid, J.L., Meredith, P.A. and Pasanisi, F. (1985) Clinical Pharmacological Aspects of Calcium Antagonists and Their Therapeutic Role in Hypertension. *Journal of Cardiovascular Pharmacology*, **7**, S18-S20. https://doi.org/10.1097/00005344-198507004-00004

[10] Sadeek, S.A., Zordok, W.A., El-Attar, M.S. and Ibrahim, M.S. (2015) Spectroscopic, Structural, Thermal and Antimicrobial Studies of 4, 6-Bis (4-Chlorophenyl)-2-Oxo-1, 2-Dihydropyridine-3-Carbonitrile with Some Transition Metals. *Bulletin of the Chemical Society of Ethiopia*, **29**, 75-94. https://doi.org/10.4314/bcse.v29i1.7

[11] Nkosi, S.M., Anand, K., Anandakumar, S., Singh, S., Chuturgoon, A.A. and Gengan, R.M. (2016) Design, Synthesis, Anticancer, Antimicrobial Activities and Molecular Docking Studies of Novel Quinoline Bearing Dihydropyridines. *Journal of Photochemistry and Photobiology B: Biology*, **165**, 266-276. https://doi.org/10.1016/j.jphotobiol.2016.10.009

[12] Upadhyay, S.K., Singh, R., Kumar, P., Singh, M., Yadav, M., Kumar, V., Aggarwal, D. and Sehrawat, N. (2019) *In Vitro* Antitubercular Activity of Dihydropyridine-Dicarboxamide and Pyrazole Derivatives against *Mycobacterium Tuberculosis*. *Bulletin of Pure & Applied Sciences-Zoology*, **38**, 102-109. https://doi.org/10.5958/2320-3188.2019.00011.1

[13] Khadilkar, B.M., Gaikar, V.G. and Chitnavis, A.A. (1995) Aqueous Hydrotrope Solution as a Safer Medium for Microwave Enhanced Hantzsch Dihydropyridine Ester Synthesis. *Tetrahedron Letters*, **36**, 8083-8086. https://doi.org/10.1016/0040-4039(95)01680-g

[14] Öhberg, L. and Westman, J. (2001) An Efficient and Fast Procedure for the Hantzsch Dihydropyridine Synthesis Under Microwave Conditions. *SYNLETT*, No. 8, 1296-1298. https://doi.org/10.1055/s-2001-16043

[15] Agarwal, A. and Chauhan, P.M.S. (2005) Solid Supported Synthesis of Structurally Diverse Dihydropyrido [2, 3-*d*] Pyrimidines Using Microwave Irradiation. *Tetrahedron Letters*, **46**, 1345-1348. https://doi.org/10.1016/j.tetlet.2004.12.109

[16] Ji, S., Loh, T., Jiang, Z. and Lu, J. (2004) Facile Ionic Liquids-Promoted One-Pot Synthesis of Polyhydroquinoline Derivatives under Solvent Free Conditions.

SYNLETT, No. 5, 831-835. https://doi.org/10.1055/s-2004-820035

[17] Phillips, A.P. (1949) Hantzsch's Pyridine Synthesis. *Journal of the American Chemical Society*, **71**, 4003-4007. https://doi.org/10.1021/ja01180a037

[18] Breitenbucher, J.G. and Figliozzi, G. (2000) Solid-Phase Synthesis of 4-Aryl-1, 4-Dihydropyridines via the Hantzsch Three Component Condensation. *Tetrahedron Letters*, **41**, 4311-4315. https://doi.org/10.1016/s0040-4039(00)00660-2

[19] Kaur, M., Priya, A., Sharma, A., Singh, A. and Banerjee, B. (2022) Glycine and Its Derivatives Catalyzed One-Pot Multicomponent Synthesis of Bioactive Heterocycles. *Synthetic Communications*, **52**, 1635-1636. https://doi.org/10.1080/00397911.2022.2090262

[20] Sabitha, G., Reddy, G.S.K.K., Reddy, C.S. and Yadav, J.S. (2003) A Novel TMSI-Mediated Synthesis of Hantzsch 1, 4-Dihydropyridines at Ambient Temperature. *Tetrahedron Letters*, **44**, 4129-4131. https://doi.org/10.1016/s0040-4039(03)00813-x

[21] Ko, S., Sastry, M.N.V., Lin, C. and Yao, C. (2005) Molecular Iodine-Catalyzed One-Pot Synthesis of 4-Substituted-1, 4-Dihydropyridine Derivatives *via* Hantzsch Reaction. *Tetrahedron Letters*, **46**, 5771-5774. https://doi.org/10.1016/j.tetlet.2005.05.148

[22] Wang, L., Sheng, J., Zhang, L., Han, J., Fan, Z., Tian, H. and Qian, C. (2005) Facile $Yb(OTf)_3$ Promoted One-Pot Synthesis of Polyhydroquinoline Derivatives through Hantzsch Reaction. *Tetrahedron*, **61**, 1539-1543. https://doi.org/10.1016/j.tet.2004.11.079

[23] Keyhani, A. and Hatamjafari, F. (2013) Synthesis of 1, 4-Dihydropyridine Derivatives Using FeCl3 as Catalyst under Solvent-Free Condition. *Oriental Journal of Chemistry*, **29**, 783-785. https://doi.org/10.13005/ojc/290260

[24] Ko, S. and Yao, C. (2006) Ceric Ammonium Nitrate (CAN) Catalyzes the One-Pot Synthesis of Polyhydroquinoline *via* the Hantzsch Reaction. *Tetrahedron*, **62**, 7293-7299. https://doi.org/10.1016/j.tet.2006.05.037

[25] Adharvana Chari, M. and Syamasundar, K. (2005) Silica Gel/$NaHSo_4$ Catalyzed One-Pot Synthesis of Hantzsch 1, 4-Dihydropyridines at Ambient Temperature. *Catalysis Communications*, **6**, 624-626. https://doi.org/10.1016/j.catcom.2005.03.010

[26] Donelson, J.L., Gibbs, R.A. and De, S.K. (2006) An Efficient One-Pot Synthesis of Polyhydroquinoline Derivatives through the Hantzsch Four Component Condensation. *Journal of Molecular Catalysis A*: *Chemical*, **256**, 309-311. https://doi.org/10.1016/j.molcata.2006.03.079

[27] Safari, J., Banitaba, S.H. and Dehghan Khalili, S. (2011) Cobalt Nanoparticles Promoted Highly Efficient One Pot Four-Component Synthesis of 1, 4-Dihydropyridines Under Solvent-Free Conditions. *Chinese Journal of Catalysis*, **32**, 1850-1855. https://doi.org/10.1016/s1872-2067(10)60295-1

[28] Tajbakhsh, M., Alaee, E., Alinezhad, H., Khanian, M., Jahani, F., Khaksar, S., Rezaee, P. and Tajbakhsh, M. (2012) Titanium Dioxide Nanoparticles Catalyzed Synthesis of Hantzsch Esters and Polyhydroquinoline Derivatives. *Chinese Journal of Catalysis*, **33**, 1517-1522. https://doi.org/10.1016/s1872-2067(11)60435-x

[29] Yang, S., Zhao, F., Lü, H., Deng, J. and Zhang, Z. (2012) An Eficient One-Pot Synthesis of 1, 4-Dihydropyridines Catalyzed by Magnetic Nanocrystalline Fe_3O_4. *Journal of Heterocyclic Chemistry*, **49**, 1126-1129. https://doi.org/10.1002/jhet.953

[30] Dam, B., Nandi, S. and Pal, A.K. (2014) An Efficient 'On-Water' Synthesis of 1, 4-Dihydropyridines Using $Fe_3O_4@SiO_2$ Nanoparticles as a Reusable Catalyst. *Tetrahedron Letters*, **55**, 5236-5240. https://doi.org/10.1016/j.tetlet.2014.08.002

[31] Alinezhad, H. and Mohseni Tavakkoli, S. (2014) Cu-Doped ZnO Nanocrystalline Powder as a Catalyst for Green and Convenient Multi-Component Synthesis of 1, 4-Dihydropyridine. *Research on Chemical Intermediates*, **41**, 5931-5940. https://doi.org/10.1007/s11164-014-1712-8

[32] Bajaj, S.D., Tekade, P.V., Lakhotiya, G.V. and Borkar, P.G. (2017) Microwave Assisted Fast Synthesis of CuO Nanoflakes: Catalytic Application in the Synthesis of 1, 4-Dihydropyridine. *Acta Physica Polonica A*, **132**, 1294-1300. https://doi.org/10.12693/aphyspola.132.1294

[33] Dehghanizadeh, Z. and Bauzar, F. (2018) Catalytic Effect of Green Zinc Oxide Nanoparticles on Multicomponent Reactions. *International Journal of Heterocyclic Chemistry*, **8**, 18-25.

[34] Bhaskaruni, S.V.H.S., Maddila, S., van Zyl, W.E. and Jonnalagadda, S.B. (2019) Four-Component Fusion Protocol with NiO/ZrO_2 as a Robust Recyclable Catalyst for Novel 1, 4-Dihydropyridines. *ACS Omega*, **4**, 21187-21196. https://doi.org/10.1021/acsomega.9b02608

[35] Cahyana, A.H., Liandi, A.R., Safitri, Y. and Yunarti, R.T. (2020) Synthesis of 1, 4-Dihydropiridine with Aromatic of Cinnamaldehyde Compound Using $NiFe_2o_4$ Mnps Catalyst and the Activity Test as Antioxidant. *Rasayan Journal of Chemistry*, **13**, 1491-1497. https://doi.org/10.31788/rjc.2020.1335700

[36] Mathur, R., Negi, K.S., Shrivastava, R. and Nair, R. (2021) Recent Developments in the Nanomaterial-Catalyzed Green Synthesis of Structurally Diverse 1, 4-Dihydropyridines. *RSC Advances*, **11**, 1376-1393. https://doi.org/10.1039/d0ra07807g

Appendix